REMARKS

Status of the Claims

Claims 1-44 were withdrawn from consideration and are now canceled. Claim 45 is amended, new claim 83 is added, and claims 58-59, and 70-82 are cancelled without prejudice to future prosecution. Therefore, with entry of this amendment, claims 45-57, 60-69, and 83 are pending.

Support for the amendments to claim 45 may be found, for example, in claims 58-59 as originally filed. Support for new claim 83 may be found in Figure 7, compound (3). Therefore, no new matter is entered with this amendment.

Claims 45-67 and 70-82 stand rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement. Claims 45-48, 54-59, 61-65, 70, 71, and 72 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-57 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349. Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of Gaster *et al.*, U.S. Patent No. 6,235,758 (hereinafter referred to as "Gaster"). Claims 45-82 also stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claim 22 of US Patent 6,495,550.

Rejection under 35 U.S.C. §112, first paragraph

Introduction

Claims 45-67 and 70-82 stand rejected as allegedly containing subject matter that was not enabled by the specification as originally filed.

Applicants note that while claims 45-67 and 70-82 stand rejected as allegedly lacking enablement, no reasonable basis has been established to question the enablement of claims 59-67 as originally filed. See MPEP § 2164.04 ("In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement

provided for the claimed invention."). The Examiner has merely asserted that the application does not provide enablement for "all compounds broadly claimed as being able 'to increase ion flow through KXNQ potassium channels' or even the compound of claims 58 or 70 because each of the variables in these claims can be any aryl group, any and all heteroaryl moieties under the sun." Office Action, page 3.

To expedite prosecution, claim 45 has been amended to include the compound set forth in original claim 59. Therefore, the Examiner's enablement rejection with respect to original claims 45 - 58 are now moot. Because no explanation has been set forth as to why the claim 59 (the limitations of which are now set forth in amended claim 45) is not adequately enabled by the disclosure, Applicants respectfully request withdrawal of the rejection in light of Applicants' amendment. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

Moreover, Applicants respectfully assert that amended claim 45 is fully enabled because:

(1) Amended claim 45 is more narrow in scope than the disclosure in Gaster that, as a prior art reference, is presumed to be enabled and operable until shown otherwise. MPEP § 2121;

(2) The specification sets forth a large number of structurally diverse KCNQ channel openers commensurate with the scope of amended claim 45;

(3) Only routine experimentation is required to practice the invention set forth in amended claim 45; and

(4) A working example of in vivo treatment of anxiety is provided in the specification.

Rejection of a claim as lacking enablement and as obvious over the prior art is improper

The Examiner states that claims 58 and 70 are not enabled "because each of the variables in these claims can be any aryl group, any and all heteroaryl moieties under the sun." Office Action, page 5. But Gaster discloses indole derivatives containing P^1 and P^2 moieties that are defined as "phenyl, aromatic or partially saturated monocyclic or bicyclic heterocyclic rings

containing up to three heteroatoms selected from nitrogen, oxygen or sulphur." See Col. 1, lines 47-51. As prior art references, Gaster's indole derivatives (which include variables defined as virtually any aromatic or heterocyclic ring) are presumed to be enabled and operable until shown otherwise. MPEP § 2121.

Amended claim 45 explicitly defines Ar^1 as one of only seven possible cyclic moieties: phenyl, 2-indolyl, benzofuranyl, furanyl, thienyl, isothiazolyl, and pyrazolyl. Therefore, if Gaster's broadly defined indole derivatives are enabled, it cannot be fairly asserted that amended claim 45, which explicitly recites specific cyclic groups, is not enabled. Because it is improper for the Examiner to assert that the cited prior art references are enabling, but that amended claim 45 is not, Applicants respectfully request withdrawal of the enablement rejection.

The law regarding fulfillment of the enablement requirement

The Examiner is respectfully reminded that routine screening of even large numbers of samples does not constitute undue experimentation under *Wands*. "The test is not merely quantitative, since ***a considerable amount of experimentation is permissible, if it is merely routine***, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988) (emphasis added).

In *Wands*, the Federal Circuit held that the specification was enabling and found that "there was considerable direction and guidance" in the specification; there was "a high level of skill in the art at the time the application was filed;" and "all of the methods needed to practice the invention were well known" *Wands* at 1406. The same is true of the present application. Indeed, the patentee in *Wands* made experimental attempts to identify 143 "high-binding" hybridomas from 10 myeloma-B lymphocyte fusions (of which four fusions completely failed), and then identified only four hybridomas of interest from the 143 "high binders." *Wands* at 1405. The applicant in *Wands* carried out the procedure for making a monoclonal antibody three times and each time successfully produced at least one such antibody. Although the Applicant in *Wands* performed what might be considered as a considerable amount of experimentation, this

quantity of experimentation is permissible under the enablement requirement, since the experimentation is merely routine and not undue.

Furthermore, as stated by the MPEP § 2164.02, the presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure. Because only an enabling disclosure is required, Applicant need not describe all actual embodiments. For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient. The present application has certainly complied with this standard.

To make a valid rejection, the Examiner must state why one would not expect to be able to extrapolate the example across the entire scope of the claims. MPEP § 2164.02. However, the Examiner has not provided convincing evidence why one of skill in the art would not be able to use the same assays used to identify the compounds of Example 1 to identify and use additional compounds commensurate in scope with the claims.

Finally, the presence of inoperative embodiments in the scope of the claim does not render a claim lacking enablement if only routine experimentation is required to determine which embodiments are operative. MPEP § 2164.08(b).

The breadth of the claims is commensurate with the disclosure

The specification sets forth a large number of structurally diverse KCNQ channel openers commensurate with scope of amended claim 45. For example, compounds having the following Ar^1 moieties are specifically disclosed in Figure 7: oxazolyl, furanyl amides, thiazolyl, thiadiazolyl, isothioazolyl, imidazolyl, pyrazolyl, triazolyl, thiophenyl, indolyl, purinyl , benzoimidazolyl, benzofuranyl, benzothiophenyl, benzoisothiazolyl, and benzylamidyl.

In addition to the KCNQ channel openers set forth in Figure 7, the specification also discloses a diverse array of KCNQ channel openers set forth in USSN 60/158,712, filed October 8, 1999, from which the current application claims priority. USSN 60/158,712 discloses a variety of N-aryl, N-alkyl, and N-cycloalkyl pyrazole amide KCNQ channel openers. Applicants have submitted herewith a signed declaration by Dr. Douglas S. Krafte. In his

declaration, Dr. Krafte confirms that any one of these channel openers can be routinely tested for the ability to treat anxiety, using the assays disclosed in the invention. Applicants respectfully note that a declaration is itself evidence that must be considered. See MPEP § 2164.05.

Only routine experimentation is required to practice the invention set forth in amended claim 45

Not only is the breadth of amended claim 45 commensurate with the disclosure, but the experimentation required to practice the full scope of amended claim 45 is merely routine.

The specification sets forth a number of simple assays to identify KCNQ channel openers. The assays involve the *in vivo* or *in vitro* treatment of a sample containing a KCNQ channel with a potential KCNQ channel opener and subsequent measurement of the KCNQ potassium channel activity. See specification, page 23, lines 25-29. The activity of the test compound may then be compared with untreated control samples. See specification, page 23, lines 27-29. Such assays can be conducted using high throughput screening methods and large libraries of chemical compounds, which are well known in the art, and systematic screening of potential KCNQ channel openers can be aided by robotic automation. See specification, page 25, lines 21-27. KCNQ potassium channel opening activity may be determined by measuring changes in ion flux through detection of cell or membrane polarization. See specification, page 24, lines 4-6. Cell or membrane polarization is detected by measuring changes in current using standard techniques such as voltage clamps or patch clamps. See specification, page 24, lines 6-10. These assays can be used routinely to determine whether or not a selected compound acts as a KCNQ channel opener.

Other standard assays for measuring ion flux are also disclosed, such as those involving the measurement of potassium or rubidium ions flux by directly detecting the concentration changes of the ions (e.g., radioisotopic labeling). See specification, page 24, lines 23-32. In addition, ion flux may be measured by determining changes in physiological conditions, such as transmitter release (e.g., dopamine), hormone release (e.g., insulin), transcriptional changes to both known and uncharacterized genetic markers (e.g., northern blots),

cell volume changes (e.g., in red blood cells), immunoresponses (e.g., T cell activation), changes in cell metabolism such as cell growth or pH changes, and changes in intracellular second messengers such as Ca^{2+}, or cyclic nucleotides. See specification, page 24, line 30 to page 25, line 8.

At page 23, lines 12-18, the specification further provides an array of methods useful in identifying KCNQ channel openers, including:

> measuring current; measuring membrane potential; measuring ion flux; e.g., potassium or rubidium; measuring potassium concentration; measuring second messengers and transcription levels, using potassium-dependent yeast growth assays; measuring pain responses in mice, e.g., with formalin algesia or hotplate assays; measuring ligand binding; and using, e.g., voltage-sensitive dyes, radioactive tracers, and patch-clamp electrophysiology.

Moreover, the assays set forth in the specification were well known in the art at the time of filing the application. The fact that these methods were well known in the art is supported by the references cited in the specification, such as:

> Ackerman *et al., New Engl. J. Med.* 336:1575-1595 (1997);
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> Hamil *et al., Pflugers. Archiv.* 391:85 (1981);
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> Vestergarrd-Bogind *et al., J. Membrane Biol.* 88:67-75 (1988);
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> Daniel *et al., J. Pharmacol. Meth.* 25:185-193 (1991);
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> Holevinsky *et al., J. Membrane Biology* 137:59-70 (1994);
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> Blatz *et al., Nature* 323:718-720 (1986); and
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> Park, *J. Physiol.* 481:555-570 (1994).

The specification also sets forth simple assays to test potassium channel openers for their ability of treat anxiety. Again, these assays can be used routinely to identify operable embodiments of the invention. On page 12, line 16 to page 13, line 3, the specification provides a detailed description of assays useful in testing anxiolytic effects:

> The standard test in rat to measure anxiolytic effect (Geller conflict procedure) was designed by Geller and Seifter and modified by Pollard and Howard (Geller & Seifter, *Psychophamracologia* 1:482-492 (1960: Pollard & Howard, *Psychopharmacology* 62:117-121 (1979)). The anxiety-reducing effect of a KCNQ2/3 channel opener was measured using the Geller conflict procedure in rats. Rats are trained to press a lever to receive food pellets during daily 1 hour sessions. The sessions are divided into punished and unpunished phases. During the four, three-minute punished periods, a light signals that each lever press will produce both a pellet and a foot shock (punishment), which reduces lever pressing. The number of punished lever presses on test days (when test compound is administered) is compared to the mean on baseline days. The positive control, chlordiazepoxide, increases punished lever pressing by > 50%. A compound that produces an increase of approximately 40% or greater is generally considered to be of interest as a rapid-onset anxiolytic. A selective KCNQ2/3 channel opener increased punished responding in a dose dependent, statistically significant manner (Figure 6).

These assays are well known in the art, as evidenced by the multiple citations in the above passage.

Although the Examiner states that the Geller test "only provides one skilled in the art with a showing of how a rat reacts with a hot plate," the Examiner has not questioned the validity of these methods or provided reasoning as to why one skilled in the art would doubt the usefulness of the disclosed assays. Office Action, page 4.

Moreover, As evidence of the routine nature of these disclosed assays, Applicants have attached hereto the declaration of Dr. Mark Krafte, who states that the Geller assay is an art accepted model for testing anxiety compounds. Dr. Krafte further states that one skilled in the art need only practice routine assays generally known in the art and explicitly disclosed in the specification to practice the invention as set forth in amended claim 45. Moreover, Dr. Krafte declares that he is not aware of any reasoning or evidence as to why one skilled in the art would

doubt the usefulness of the disclosed assays. The Examiner is respectfully reminded that a declaration is itself evidence that must be considered. See MPEP § 2164.05.

Thus, Applicants assert that one skilled in the art, using the teachings in the specification and methods generally known in the art, would be able to determine the ability of KCNQ channel openers to treat anxiety in a subject. Absent some reasoning or evidence to doubt the usefulness of the methods disclosed in the specification, Applicants submit that one skilled in the art would recognize that Applicants fully enabled a methods of identifying a KCNQ potassium channel opener useful in treating anxiety.

A working example of in vivo treatment of anxiety

The specification provides a working example of the claimed invention in which a KCNQ channel opener is administered in accordance with the protocol of the Geller conflict model. See Example 6. As pointed out by Dr. Krafte in his expert declaration, this example demonstrates that the invention as claimed works for its intended purpose. The Examiner has presented no evidence or reasoning as to why one skilled in the art would doubt the validity of this experiment. Moreover, the Examiner has presented no evidence or reasoning as to why one skilled in the art, after examining this experiment, would conclude that a KCNQ channel opener would ***not*** work as intended in claims 45-57.

Therefore, Applicants respectfully submit that one skilled in the art would recognize that Applicants enabled a method of reducing anxiety using a compound that increases ion flow through a KCNQ potassium channel as claimed.

Rejections under 35 U.S.C. §103(a)

Claims 45-48, 54-59, 61-65, 70, 71 and 72 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Gaster *et al.*, U.S. Patent No. 6,235,758 (hereinafter referred to as "Gaster"). The Examiner asserts that "Gaster et al. teach of aryl carbamoyl compounds that are used to treat anxiety." Office Action, page 13.

Applicants respectfully disagree. As a preliminary matter, Applicants do not agree that Gaster discloses treatment of anxiety using a compound able to increase ion flow

through KCNQ potassium channels. Even assuming *arguendo* that Gaster does make that disclosure, Gaster does not teach all the structural elements of the chemical genus of amended claim 45. Applicants note that Gaster does not teach the use of ***all*** aryl carbamoyl compounds. Rather, Gaster discloses only a genus of aryl carbamoyl compounds as set forth at Col. 1, line 34, to Col. 6, line 44.

The genus of compounds disclosed by Gaster includes an "R^4" moiety bonded to the amide carbonyl, which corresponds to "Ar^1" in amended claim 45. The Gaster "R^4" moiety is selected from the moieties of formulae (i), (ii), and (iii). See Col. 2, lines 1-65. However, none of the moieties of formulae (i), (ii), or (iii) meet the definition of "Ar^1" set forth in amended claim 45. That is, formulae (i), (ii), or (iii) do not encompass a phenyl, 2-indolyl, benzofuranyl, furanyl, thienyl, isothiazolyl, or pyrazolyl directly linked to the amide carbonyl as recited in amended claim 45. Therefore, because Gaster does not contain all the elements of the claimed invention, Gaster cannot be used to establish a *prima facie* case of obviousness.

The Examiner is respectfully reminded that, in order to establish a *prima facie* case of obviousness, the rejection must demonstrate that (1) the cited references teach all the claimed elements; (2) there is a suggestion or motivation in the prior art to modify or combine the reference teachings; and (3) there is a reasonable expectation of success. MPEP § 2143; *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991).

Double Patenting Rejection

The Examiner has rejected claims 45-57 under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349. Claims 45-82 stand rejected under the judicially created obviousness-type double patenting as allegedly unpatentable over claims 46-67 of Gaster *et al.*, U.S. Patent No. 6,235,758. Claims 45-82 also stand rejected under the judicially created obviousness-type double patenting as allegedly obvious over claim 22 of US Patent 6,495,550.

With respect to the rejection over claims 46-67 of McNaughton-Smith *et al.*, U.S. Patent No. 6,593,349, Applicants respectfully submit that the rejection is now moot in light of

the amendment to claim 45. Applicants have amended claim 45 to include the limitation of claim 59. Because claim 59 was not rejected over claims 46-67 of U.S. Patent No. 6,593,349, Applicants respectfully request withdrawal of the rejection.

With respect to the rejection over claims 46-67 of Gaster, as argued above, the present invention is not obvious over Gaster. Therefore, Applicants request that the rejection be withdrawn.

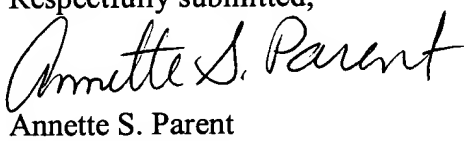
With respect to the rejection over claim 22 of US Patent 6,495,550, if necessary a terminal disclaimer will be filed in accordance with 37 CFR §1.321, should the claims be deemed otherwise allowable. Until such time, Applicants request that the rejection be held in abeyance.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,



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